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Role of vasopressin in support of blood pressure in potassium deficient rats

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Role of vasopressin in support of blood pressure in potassium deficient rats. Arginine vasopressin (AVP) has been found to contribute to the maintenance of blood pressure (BP) in the rat. Since potassium deficiency results in alterations in systemic hemodynamics, the role of AVP in the control of BP was studied after 14 to 21 days of dietary potassium deficiency. When potassium deficient and control rats were allowed free access to water, plasma osmolality (301.4 ± 1 vs. 293.4 ± 3 mOsm/kg; $P < 0.02$) and plasma AVP (3.5 ± 0.2 vs. 2.4 ± 0.2 pg/ml; $P < 0.02$) were increased in potassium deficient animals. To determine the role of this increase in AVP in the maintenance of BP, BP was determined in rats made polydipsic by adding glucose to the drinking water. In both control and potassium deficient rats, increased fluid intake resulted in increased urine output, decreased urinary and plasma osmolality, and a decrease in plasma AVP. While there was no change in BP in control rats when fluid intake was increased, BP fell from 103.9 ± 1.8 to 96 ± 2.6 mm Hg ($P < 0.05$) in potassium deficient rats with increased fluid intake. To confirm that the decrease in plasma AVP caused the decrease in BP in potassium deficient rats, an AVP pressor antagonist was employed. Following the administration of the AVP pressor antagonist, there was no change in BP in control animals. In contrast, BP fell from 104.3 ± 1.9 to 98.3 ± 2.5 mm Hg; $P < 0.05$ in potassium deficient rats. In addition, vasopressin infusion in potassium deficient rats with suppressed endogenous plasma AVP resulted in the restoration of BP to that observed in potassium deficient rats with an intact vasopressin system. In summary, potassium deficiency results in an elevation in plasma AVP as a consequence of hyperosmolality. Since maneuvers which decreased either the content or action of AVP resulted in a decrease in BP in potassium deficient rats and since vasopressin infusion resulted in restoration of MAP in potassium deficient rats with suppressed endogenous plasma AVP, we conclude that AVP is important in the support of BP in the potassium deficient conscious rat.

Rôle de la vasopressine dans le maintien de la pression artérielle chez des rats carencés en potassium. Il a été montré que l'arginine vasopressine (AVP) contribue au maintien de la pression artérielle (BP) chez le rat. Puisque la carence en potassium entraîne des altérations de l'hémodynamique systémique, le rôle de l'AVP dans le contrôle de la BP a été étudié après 14 à 21 jours de carence potassique alimentaire. Quand des rats carencés en potassium et contrôles buvaient librement de l'eau, l'osmolalité plasmatique (301.4 ± 1 contre 293.4 ± 3 mOsm/kg; $P < 0.02$) et l'AVP plasmatique (3.5 ± 0.2 contre 2.4 ± 0.2 pg/ml; $P < 0.02$) étaient élevées chez les animaux carencés en potassium. Afin de déterminer le rôle de cette augmentation de l'AVP dans le maintien de la BP, la BP a été déterminée chez des rats rendus polydipsiques en ajoutant du glucose à l'eau de boisson. Chez les rats contrôles et déficients en potassium, l'augmentation de l'apport liquidien a entraîné une augmentation du débit urinaire, une diminution de l'osmolalité urinaire et plasmatique et une diminution de l'AVP plasmatique. Alors qu'il n'y avait pas de modification de BP chez les rats contrôles lorsque l'apport liquidien était augmenté, BP a diminué de 103.9 ± 1.8 à 96 ± 2.6 mm Hg ($P < 0.05$) chez les rats carencés en potassium lorsque l'apport liquidien a été augmenté. Afin de confirmer que la diminution de l'AVP plasmatique était à l'origine de la diminution de BP chez les rats carencés en potassium, un antagoniste de l'effet pressif de l'AVP a été utilisé. Aprés l'administration de l'antagoniste de l'effet pressif de l'AVP, il n'y a pas eu de modification de BP chez les animaux contrôles. A l'opposé, BP a chuté de 104.3 ± 1.9 à 98.3 ± 2.5 mm Hg; $P < 0.05$ chez les rats carencés en potassium. En outre, la perfusion de vasopressine chez des rats carencés en potassium avec AVP plasmatique endogène supprimée a entraîné la restauration de la BP à la valeur observée chez des rats déficients en potassium avec un système vasopressine intact. En résumé la carence en potassium entraîne une élévation de l'AVP plasmatique, conséquence de l'hyperosmolalite. Puisque que les manoeuvres diminuant soit le contenu soit l'action de l'AVP ont entraîné une diminution de la BP chez des rats carencés en potassium, et que la perfusion de vasopressine a restauré la MAP chez des rats déficients en potassium avec une AVP plasmatique endogène supprimée, nous concluons que l'AVP est importante pour le maintien de la BP chez le rat éveillé carencé en potassium.

Chronic potassium deficiency causes marked changes in hemodynamics in the conscious rat. Although peripheral vascular resistance (PVR) decreases 30%, there is only a slight decrease (10%) in mean arterial pressure (MAP) because of an increase in cardiac output [1]. The decrease in PVR in potassium deficient rats is of particular interest since it occurs in the setting of a threefold increase in plasma renin activity [2]. This observation suggests that the pressor effect of angiotensin II is blunted in potassium deficiency [3] and raises the possibility that other pressor hormones might contribute to the maintenance of peripheral vascular resistance, and therefore MAP, in potassium deficient animals.

Arginine vasopressin (AVP) is a pressor hormone which may contribute to the increase in MAP in some forms of hypertension [4–6]. In addition, AVP has recently been demonstrated to contribute to the maintenance of MAP during hemorrhage [5–9] and water deprivation [10, 11]. The increase in AVP following these maneuvers is the result of nonosmotic and osmotic release of AVP, respectively. Since potassium deficiency is associated with a renal concentrating defect [12] (osmotic stimulus) as well as a decrease in PVR and MAP (nonosmotic stimulus), it might be anticipated that plasma AVP would be elevated in the potassium deficient animal. The purpose of the present study was to determine the role of AVP in the support of blood pressure in the conscious potassium deficient rat.

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Methods

Studies were performed in Sprague-Dawley rats (Charles River Breeding Laboratories, Wilmington, Massachusetts) weighing 190 to 250 g at the initiation of the study. Experimental animals were fed a potassium deficient diet (ICN Nutritional Biochemicals, Cleveland, Ohio) containing Na, 150 mEq/kg; K, 10 mEq/kg; Cl, 620 mEq/kg; Ca, 235 mEq/kg; PO_4, 1.8 g/kg; and Mg, 330 mEq/kg for 14 to 21 days. Control rats were fed an identical diet to which has been added KCl, K_2HPO_4, and KH_2PO_4 to yield a final content of Na, 160 mEq/kg; K, 240 mEq/kg; Cl, 740 mEq/kg; Ca, 210 mEq/kg; PO_4 5.9 g/kg; and Mg, 339 mEq/kg. Rats had free access to food and water.

Effects of potassium deficiency on MAP and plasma AVP

To obtain hemodynamic measurements, animals were anesthetized with ether, and polyethylene catheters (PE-50) were placed in the femoral artery and vein for direct arterial pressure monitoring and blood sampling, respectively. During surgery (10 min) rats were given volume replacement of 0.5% body weight with isotonic saline. Following surgery, animals were placed in restraining cages and allowed to recover in a quiet room for a minimum of 60 min. MAP was then measured using a Bell and Howell pressure transducer (type 4-327-I) and Gilson polygraph (Gilson Medical Electronics, Middletown, Wisconsin). After MAP determinations, blood was obtained for determination of potassium and osmolality. For determination of plasma vasopressin and renin activity, additional groups of rats were placed on similar dietary protocols and then sacrificed by decapitation.

Plasma and urine sodium and potassium were determined by flame photometer (Instrumentation Laboratory, model 343, Lexington, Massachusetts) and plasma and urine osmolality by freezing point depression (Advanced Instruments Osmometer, model 3W, Neeham Heights, Massachusetts). Plasma AVP and renin activity were measured by radioimmunoassay [13, 14].

Effects of increased fluid intake on MAP and plasma AVP

To study the role of AVP in support of MAP, AVP release was suppressed by increasing fluid intake accomplished through the addition of glucose to the drinking water to stimulate taste. Potassium deficient rats rapidly increased fluid intake when 2.5% glucose was added to the drinking water for 2 days. Control rats were more resistant to attempts to stimulate thirst. To cause significant increases in fluid intake, control rats were given 5% glucose in the drinking water for 7 to 8 days. During the period of glucose water feeding, rats were individually housed in metabolic cages which permitted the separation of urine and feces. Rats were accepted for further study only if water intake was increased by more than 80%. For comparison, control and potassium deficient rats that drank water were also studied under metabolic conditions. Measurements of food and fluid intake and urine output were made for each 24-hr period. Aliquots of urine samples were obtained for the measurement of sodium, potassium, and osmolality. In addition, all urine samples were checked for the presence of glucose by a glucose oxidase dipstick method (Clinistix, Ames Company, Elkhart, Indiana). No animal in any group developed glycosuria.

At the end of this period, MAP was measured as described above. Samples of blood were then obtained for measurement of potassium and osmolality. For determination of plasma vasopressin and renin activity, additional groups of rats were placed on similar dietary protocols and then sacrificed by decapitation.

Effects of AVP pressor antagonist

Further studies of the role of AVP in blood pressure support were performed with the use of an antagonist of the pressor action of vasopressin, [1-(β-mercapto-β, β-cyclopentamethylenepropionic acid), 2-(0-methyl) tyrosine] arginine vasopressin [$d(CH_2)_5$ Tyr(Me) AVP] [15]. To demonstrate that the AVP antagonist was effective in the dose employed, preliminary studies were performed in six control rats. The pressure response to 10 mU exogenous vasopressin (Pitressin, Parke Davis, Detroit, Michigan) was determined before and after the administration of the AVP antagonist given as an intravenous bolus of 10 μg/kg. After determining the efficacy of the AVP antagonist, the drug was administered to ten control and six potassium deficient rats following surgical preparation as described above. For these studies, rats had received their usual water intake until the time of study. Additional studies using the AVP antagonist were performed in potassium deficient rats with suppressed vasopressin levels (see below) secondary to increased fluid intake as described above. For these studies, the AVP antagonist was administered to four potassium deficient rats drinking 2.5% glucose.

Effects of vasopressin infusion in potassium-deficient rats with increased fluid intake

In a final group of studies vasopressin was infused into potassium deficient rats with suppressed AVP levels secondary to increased fluid intake. For these studies seven potassium deficient rats were prepared as described in the section on the effects of increased fluid intake on MAP. MAP was determined and vasopressin was infused at 8 μU/min/100 g body weight for 1 hr (1 cc total volume) after which MAP was recorded and blood was obtained for plasma AVP determination. In preliminary studies we had determined that this dose of vasopressin resulted in plasma AVP levels of 3 to 4 pg/ml. For comparison, MAP and plasma AVP levels were also determined in five potassium deficient rats with usual fluid intake which had been prepared for surgery and infused for 1 hr with the same volume of 0.45 M saline as that utilized in the vasopressin infusion group.

Results are expressed as mean ± SE. Statistical comparisons were made by the unpaired t test or one-way analysis of variance with Duncan's multiple range test [16].

Results

Effects of potassium deficient diet on MAP and plasma AVP

At the time of study, plasma potassium was 3.95 ± 0.3 mEq/liter in control rats and 2.24 ± 0.32 mEq/liter in potassium deficient rats ($P < 0.001$). Previous studies from our laboratory using the identical diet have shown significant decreases in muscle and kidney potassium content after 14 to 21 days of dietary potassium deficiency [1, 2].

Table 1 and Figure 1 demonstrate the effect of potassium deficiency on plasma osmolality and AVP. Since not all determinations could be performed in each animal, the number of rats available for each determination is indicated. Plasma

Table 1. Effect of potassium deficiency on plasma osmolality (P_{Osm})

	Final 24-hr			
	Intake *ml*	Urine volume *ml*	U_{Osm} *mOsm/kg*	P_{Osm} *mOsm/kg*
Control	43.2 ± 1.5	23.7 ± 1.5	1840 ± 70	293.4 ± 3
N	12	12	12	10
Control with increased fluid intake	115 ± 5.8	76.8 ± 7	256 ± 41	292.1 ± 1.2
N	8	8	8	8
Potassium deficient[a]	67.7 ± 4.7[b]	55 ± 4.5[b]	605 ± 51[c]	301.4 ± 1[b]
N	13	13	13	11
Potassium deficient with increased fluid intake[b]	118 ± 11.4[c]	102.7 ± 9.7[c]	297 ± 30[e]	290 ± 2.4[b]
N	12	12	12	5

[a] Control versus potassium deficient rats, $P < 0.05$[b], $P < 0.001$[c] by one-way analysis of variance.

[d] Potassium deficient versus potassium deficient with increased fluid intake, $P < 0.05$[b], $P < 0.01$[e], $P < 0.001$[c] by one-way analysis of variance.

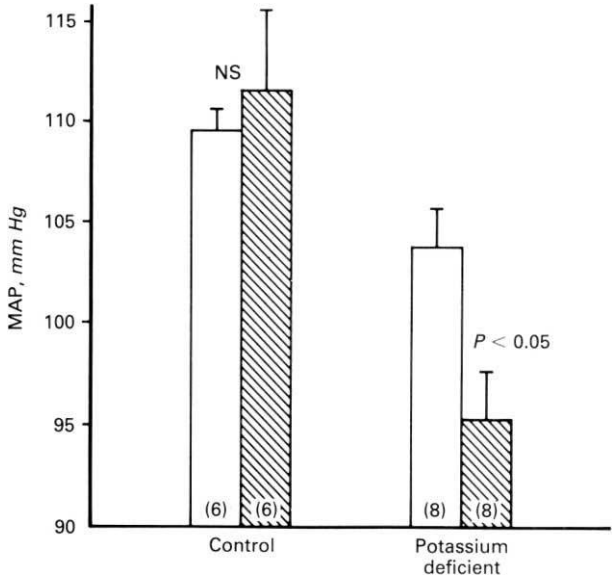

Fig. 2. *Effect of increasing fluid intake on mean arterial pressure* (MAP). *Open bars* represent usual fluid intake; *hatched bars* represent increased fluid intake. *Parentheses* indicate the number of animals studied in each group.

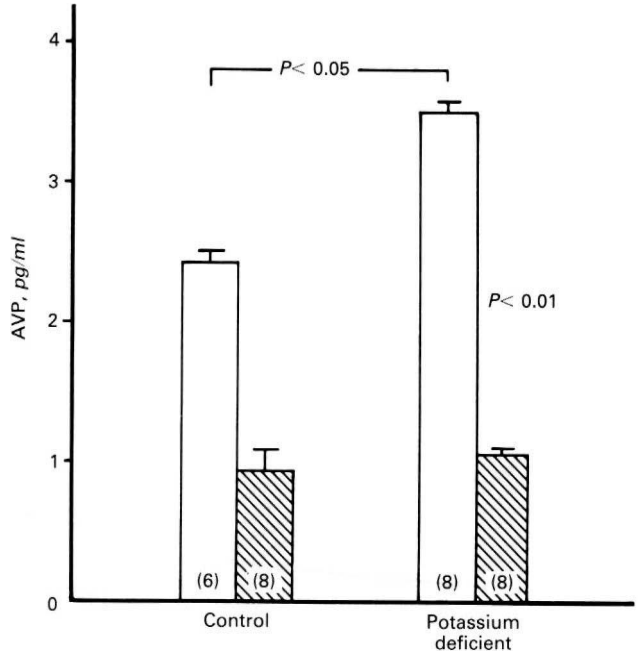

Fig. 1. *Effect of potassium deficiency on plasma arginine vasopressin* (AVP). *Open bars* represent usual fluid intake; *hatched bars* represent increased fluid intake produced by watering with glucose solutions. *Parentheses* indicate the number of animals studied in each group.

osmolality was increased in potassium deficient rats (301.4 ± 1 mOsm/kg in potassium deficiency vs. 293.4 ± 3 mOsm/kg in control; $P < 0.02$; Table 1). This increase in plasma osmolality was associated with a 46% increase in plasma AVP (3.5 ± 0.2 pg/ml in potassium deficient rats vs. 2.4 ± 0.2 pg/ml in control rats; $P < 0.02$). Despite this increase in plasma AVP in potassium deficiency, basal MAP was only 103.9 ± 1.8 mm Hg in potassium deficient rats compared to 109.5 ± 1.3 mm Hg in control rats ($P < 0.05$).

Effects of increased fluid intake on mean arterial pressure and plasma AVP

To study the role of AVP in blood pressure support and to determine whether or not the increase in plasma AVP was caused by the increase in plasma osmolality, fluid intake was increased in control and potassium deficient animals. Control rats drinking water (usual fluid intake) had fluid intake and urine volume and osmolality as shown in Table 1. In contrast, control rats drinking 5% glucose (increased fluid intake) had significantly greater fluid intake and urine output. This was associated with a lower plasma and urinary osmolality (Table 1) and a decrease in plasma vasopressin (Fig. 1). Mean arterial pressure was the same in control rats with usual fluid intake (109.4 ± 2.6 mm Hg) and those with increased fluid intake (111.7 ± 4.1 mm Hg).

As shown in Table 1, potassium deficient rats drinking 2.5% glucose (increased fluid intake) also had significantly greater fluid intake and urine output and significantly lower urine and plasma osmolality than potassium deficient rats drinking water (usual fluid intake). Moreover, in association with the decrease in plasma osmolality, plasma AVP decreased to levels which were similar to control rats with increased fluid intake: 1.05 ± 0.4 pg/ml (Fig. 1). This decrease in plasma AVP levels was associated with a decrease in MAP in potassium deficient rats: 103.9 ± 1.8 mm Hg during usual fluid intake versus 96 ± 2.6 mm Hg after increased fluid intake; $P < 0.05$ (Fig. 2). Since there was no increase in osmolar excretion (U_{OsmV}) or change in sodium balance or plasma renin activity in glucose-drinking potassium deficient rats (Table 2), it is likely that the decrease in MAP was caused by the decrease in plasma AVP.

Table 2. Effect of glucose drinking on solute excretion, sodium balance, and plasma renin in potassium deficient rats

	$U_{Osm}V$ *mOsm/48°*	Net Na balance *μEq/48°*	PRA *ng/ml/hr*
Potassium deficient $N = 8$	59.5 ± 2.6	1190 ± 375	11.48 ± 2.2
Potassium deficient drinking 2.5% glucose $N = 6$	51.0 ± 2.0 $P < 0.05$	1260 ± 332 NS	10.48 ± 1.4 NS

Abbreviations: NS, no significant difference; PRA, plasma renin activity.

Effects of AVP pressor antagonist on mean arterial pressure

To confirm that a decrease in plasma AVP results in a decrease in MAP in potassium deficient rats, further studies were performed with an AVP pressor antagonist. In the dose used, the AVP antagonist completely blocked the pressor response to 10 mU exogenous vasopressin in normal rats. MAP increased 39.6 ± 3.3 mm Hg after AVP alone, but only 0.8 ± 1.2 mm when AVP was given after the antagonist. Administration of the AVP antagonist did not produce change in blood pressure in control rats (Fig. 3). In contrast, administration of the AVP antagonist produced a significant fall in MAP in potassium deficient rats, from 104.3 ± 1.9 mm Hg to 98.3 ± 2.5 mm Hg; $P < 0.05$). Furthermore, when the antagonist was administered to potassium deficient rats with suppressed vasopressin levels secondary to increased fluid intake, there was no further fall in blood pressure (Fig. 4).

Effects of vasopressin infusion in potassium deficient rats with increased fluid intake

To further determine the role of AVP to support MAP in potassium deficiency, vasopressin was infused into potassium deficient rats with suppressed plasma AVP levels secondary to increased fluid intake. Figure 5 demonstrates that when vasopressin was infused to provide plasma AVP levels (3.26 ± 0.3 pg/ml) comparable to potassium deficient rats with the usual fluid intake (3.64 ± 0.6 pg/ml), MAP increased by 8.5 ± 1.1 mm Hg and was not different than potassium deficient rats with usual fluid intake.

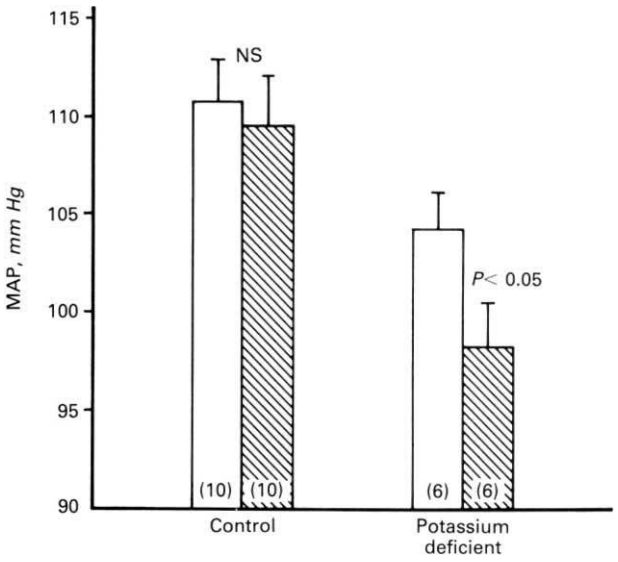

Fig. 3. *Effect of the AVP pressor antagonist $d(CH_2)_5$ Tyr(Me)AVP on MAP. Open bars* represent MAP before administration of the AVP antagonist; *hatched bars* represent MAP after administration of the antagonist. *Parentheses* indicate the number of animals studied in each group.

Discussion

In the present study, we investigated the role of arginine vasopressin in the support of blood pressure in the chronic potassium deficient rat. We utilized maneuvers which suppressed both the release of AVP and the action of AVP on vascular smooth muscle. Both approaches provided evidence that vasopressin supports blood pressure in the conscious potassium deficient rat.

Potassium deficiency resulted in an elevation of plasma vasopressin levels. There are at least four possible mechanisms by which this could have occurred: *(1)* potassium deficiency results in a decrease in PVR and MAP and the subsequent nonosmotic stimulation of AVP release [17]; *(2)* potassium deficiency results in an increase in plasma renin activity and AII which resulted in AVP release [18]; *(3)* potassium deficient rats have a renal concentrating defect [12] which results in an increase in plasma osmolality and enhanced AVP release; and *(4)* potassium deficiency per se might directly stimulate AVP release. The results suggest that the increase in AVP was mediated by an osmolar stimulus. In this regard, potassium deficient rats had an increase in plasma osmolality which was corrected by increasing the fluid intake of these animals. Moreover, in association with the decrease in plasma osmolality of glucose-drinking potassium deficient rats, AVP decreased to levels comparable to control rats. This decrease in AVP occurred despite continued potassium deficiency and hyperreninemia, and was associated with a further decrease in MAP, a hemodynamic factor which would be expected to further increase AVP levels. Thus, while there are several possible mechanisms for the increase in plasma AVP in potassium deficiency, it is likely that the increase in AVP is a consequence of hyperosmolality resulting from the renal concentrating defect [12] associated with chronic potassium deficiency.

The role of the increase in vasopressin levels in potassium deficiency was first studied by suppressing AVP release. To accomplish this, animals were induced to increase their fluid intake by adding glucose to their drinking water (Table 1). Following increased fluid intake, AVP decreased in both control and potassium deficient rats. While AVP levels fell in control rats, there was no change in mean arterial pressure (Fig. 2). In marked contrast, however, suppression of plasma AVP levels in potassium deficient rats resulted in a significant decrease in MAP (Fig. 2). Furthermore, the decrease in MAP in potassium deficient rats could not be explained by changes in either sodium balance or plasma renin activity. These studies demonstrate, therefore, that vasopressin supports the MAP of potassium deficient, but not control, rats.

To further investigate the role of vasopressin in the support of

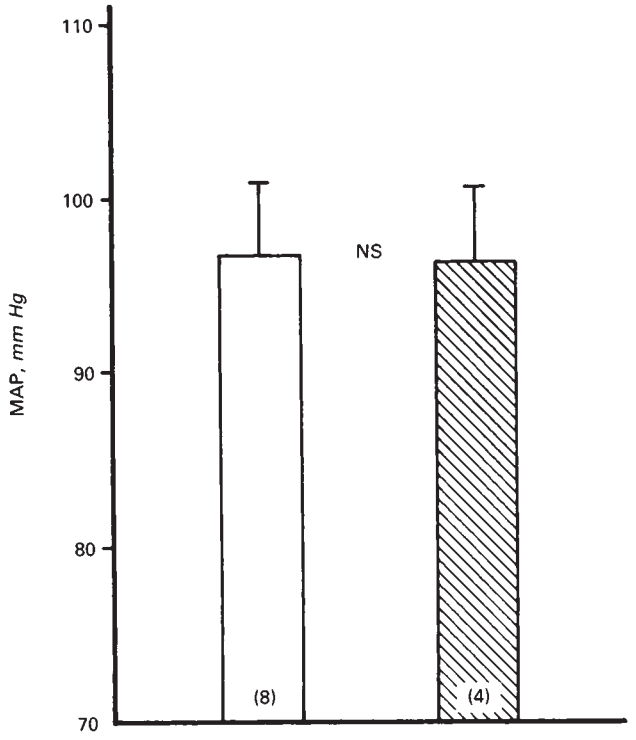

Fig. 4. *Effect of AVP pressor antagonist on MAP in potassium deficient rats with suppressed vasopressin levels.* AVP was suppressed by adding 2.5% glucose to the drinking water *(open bars). Hatched bars* represent MAP in potassium deficient rats with suppressed AVP levels after administration of the AVP antagonist. *Parentheses* indicate the number of animals studied in each group.

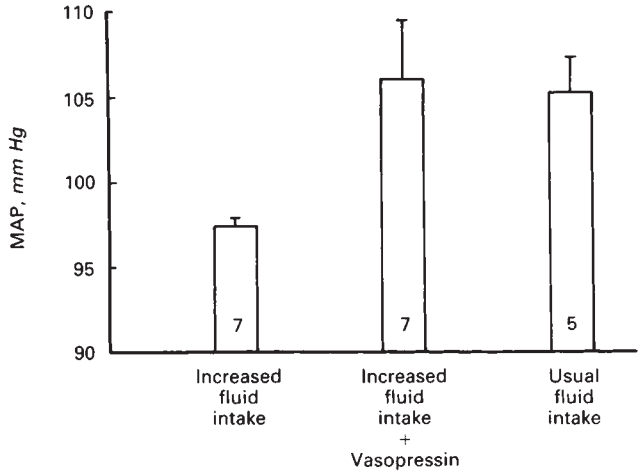

Fig. 5. *The effect of AVP infusion on MAP in potassium deficient rats with increased fluid intake.* Potassium deficient rats with increased fluid intake *(left bar)* were infused with AVP *(middle bar)* and compared to potassium deficient rats with usual fluid intake *(right bar). Parentheses* indicate the number of animals studied in each group.

blood pressure in potassium deficiency, an antagonist of the pressor action of AVP [d(CH_2)5 Tyr(Me)AVP] was employed. As has been demonstrated by other investigators [10], administration of the AVP antagonist did not produce change in MAP in control rats (Fig. 3). In contrast, administration of the AVP antagonist produced a decrease in blood pressure in potassium deficient rats similar in magnitude to the decrease in blood pressure observed when AVP release was suppressed by increasing fluid intake. In addition, when AVP levels were suppressed in potassium deficient rats by increasing their fluid intake, the AVP antagonist had no additional depressor effect. Thus, when either the content or the action of AVP is decreased, there is a decrease in MAP in potassium deficient, but not control, animals.

In the final group of studies vasopressin was administered to potassium deficient rats in which endogenous plasma AVP levels had been suppressed by inducing increased fluid intake. When plasma AVP levels were rendered comparable to potassium deficient rats with usual fluid intake, MAP was restored to the levels observed in potassium deficient rats with usual fluid intake (Fig. 5).

These three complementary studies suggest that vasopressin plays an important role in the support of blood pressure in the potassium deficient rat. Of interest is the fact that these studies demonstrate that vasopressin supports blood pressure in the normovolemic state. In other studies, the administration of an AVP pressor antagonist has been found to lower MAP following acute hemorrhage [9], and after 24 to 40 hr of water restriction [10, 11], maneuvers which would be anticipated to decrease circulating blood or plasma volume, respectively. In contrast, the potassium deficient rat is in positive sodium balance [19] and has an increased plasma volume [1].

A surprising observation in the present study was that AVP antagonism lowered MAP in potassium deficient rats despite plasma AVP levels which are generally not felt to be within the range of pressor activity of this hormone [20, 21]. Although the present study does not provide an explanation for this observation, two possibilities seem likely. Several studies have demonstrated that relatively modest elevations of AVP increase blood pressure in the absence of a functional autonomic nervous system [22, 23]. While the status of the autonomic nervous system has not been assessed in the potassium deficient rats, there is evidence that potassium deficiency results in autonomic insufficiency in potassium deficient patients [24]. Moreover, it is possible that even small increases in AVP are important to support MAP in the vasodilated potassium deficient rat since these animals are markedly resistant to another major pressor hormone, angiotensin II [3]. Further studies will be required to explore these possibilities.

The absolute magnitude of mean blood pressure fall after vasopressin removal or antagonism was moderate. However, even in the presence of AVP, MAP was decreased in potassium deficient rats. In the absence of AVP, MAP fell to levels less than 100 mm Hg. Since the rat begins to lose its ability to autoregulate renal blood flow below 100 mm Hg [25], any decrease in MAP below this value might be expected to compromise renal function. This is particularly important in potassium deficiency since renal blood flow is only 50% of the value obtained in normal animals [1].

In summary, potassium deficiency in the rat results in a decrease in mean arterial pressure and an increase in plasma osmolality and plasma AVP. Following increased fluid intake, both plasma osmolality and AVP can be normalized. In potassium deficient, but not control, rats reduction of the plasma level of vasopressin or antagonism of its action results in a further

decrease in mean arterial pressure. In potassium deficient rats with suppressed endogenous vasopressin levels, vasopressin infusion results in restoration of MAP to values observed in potassium deficient rats with an intact vasopressin system. We conclude that an increase in plasma osmolality mediates the increase in AVP levels and that arginine vasopressin contributes support of systemic arterial pressure in the conscious potassium deficient rat.

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